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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,009	04/17/2001	Ming-Qun Xu	NEB-150PUS	6390

28986 7590 05/23/2003

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,009	XU ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[·] Responsive to communication(s) filed on *31 January 2002 and 06 March 2003* .

2a)[·] This action is **FINAL**. 2b)[ ] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *12-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *12-19 and 22-33* is/are rejected.

7)[·] Claim(s) *20 and 21* is/are objected to.

8)[ ] Claim(s) are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)[ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other.

DETAILED ACTION

Response to Amendment

Applicant's cancellation of claim 7 in Amendment B, Paper No. 13 filed December 31, 2002, removes the basis for the rejections of record thereof stated in Paper No. 10 mailed July 3, 2002. The amendments of claims 12, 17, 18, 22, 25 submitted with Paper No. 13 overcome the objection of record of claim 18 and the rejections of record of claims 12-27 as indefinite under the second paragraph of 35 U.S.C. §112 as well as the rejection of record of claims 12-20 and 22-27 under the first paragraph of 35 U.S.C. §112 for lack of enablement. The Terminal Disclaimer, Paper No.16 filed March 6, 1003, is effective and removes the basis for the rejection of record of claims 12-14, 25 and 27 under the judicially created doctrine of double patenting over claims of the issued U/S. Paten No. 5,834,237. In view of the new claims 28-33 introduces with Amendment C, Paper No. 15 filed March 6, 2003, the double-patenting rejection of claim herein is maintained over claims in application serial No. 09/249,543.

Priority

Page 1 of the specification is amended in Paper No. 13 to restate Applicant's claim to priority but it is noted that copending application serial No. 09/249,543 no longer states a priority claim to U.S. application serial No. 08/811,492, issued as U.S. Patent No. 5,834,247. It is further noted that no claim for priority may be accorded if asserted to antedate the filing date of a provisional application. The instant application must either trace its priority to the September 30, 1998, filing date of provisional application serial No. 60/102,413, or trace priority through one or more U.S. utility applications sharing a co-inventor and common elements of disclosure already pending before application serial No. 08/811,492 issued as a patent on November 10, 1998. The claim asserted in Paper No. 13 is recognized only to the provisional application serial No. 60/102,413.

Claim Objections

Claim 28 is objected to because of the following informalities: the word "protein" is misspelled at line1 of the claim. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22 and 28-33 are provisionally rejected, essentially for reasons of record, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 15 and 35 of copending Application No. 09/249,543, in view of Smith et al., 1997, made of record herewith. This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other, in part because the methods of claims 22 and 28-32 herein are disclosed in the copending application and embrace, save for the use of a modified *Mth* R1R1 intein, the subject matters of claims 1 and 35 of the copending application. In addition, while claim 33 herein is not identical to claim 15 of the copending application, they are not patentably distinct from each other because a fusion protein of claim 33 herein is indistinguishable from a fusion protein of claim 15 of the copending application. Thus a patent bearing claims 1, 15 and 35 of the copending application embrace method which is a species of the genus of methods of use of a generic intein of claims 22 and 28-33 herein, which may

be a modified intein, where methods of claims in the instant application and the copending application otherwise includes processes, intermediate products, and thiol reagents disclosed herein and in the copending application. Patenting of the claims would constitute an unjustified or improper timewise extension of the "right to exclude" granted by a patent because it would have been obvious to one of ordinary skill in the art at the time the invention was made that the specific, *Mth* R1R1 intein, of Smith et al., made of record herewith, is among the generic inteins of the claims 22 and 28-33 of the instant application, a species-genus relationship, and because the fusion product that is the result of a method of claim 1 of the copending application is species of the fusion product that is result of the method of claim 22 herein.

Claim Rejections - 35 USC §§102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
>
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
>
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 12-14, 16, 25 and 27 are for reasons of record rejected under 35 U.S.C. §102(e) as being anticipated by Comb et al., U.S. Patent No. 5,834,247, of record.

Comb et al., issuing on an application filed eighteen months before the September 30, 1998, priority date accorded the instant application, disclose, see Example 19 at cols. 75-

77 and claim 96, the expression of precursor polypeptides using the pMYB129 plasmid, see Example 15 at cols. 53-56, from which they obtained 'target" proteins having a C-terminal thioester upon thiol reagent-induced cleavage of a modified *Sce* VMA intein fused at its amino terminus to the carboxyl terminus of maltose binding protein. Comb et al. further disclose the preparation of a labeled expressed protein by ligating labeled synthetic peptides having amino terminal cysteines to the C-terminal thioester of the expressed maltose binding protein wherein the labels are peptide fragments which are antigenic determinants, see Figure 29, anticipating claims 12-14, 16, 17, 25 and 27 herein. The rejection of record is sustained.

Claims 12-14, 17-19, 25 and 26 are for reasons of record rejected under 35 U.S.C. §102(b) as being anticipated by Chong et al., 1997, **Gene**, Vol. 192, pages 271-281, of record.

Chong et al., published in June 1997, thus fifteen months before the September 30, 1998, priority date accorded the instant application, disclose, see Figures 1, 4 and 5B, and section 2.6 at page 276, the expression of precursor polypeptides using the pCYB plasmid having a multiple cloning site and further providing a nucleic acid sequence encoding a chitin binding protein fused to the cleavage-resistant carboxyl terminus of the modified *Sce* VMA intein, from which they obtained expressed proteins having a C-terminal thioester upon thiol reagent-induced cleavage of a modified *Sce* VMA intein fused at its amino terminus to the carboxyl terminus of a target protein and also disclose preparation of a labeled expressed proteins by ligating a radiolabeled peptide constituting an amino terminal cysteine to the C-terminal thioester of expressed proteins, anticipating claims 12-14, 17, 18, 25 and 26 herein. The rejection of record is sustained.

Claims 12-14, 17-19, 22, 25 and 26 are rejected under 35 U.S.C. §102(a) as being anticipated by Severinov et al., 1998, **The Journal of Biological Chemistry**, Vol. 273, pages 16205-16209, of record.

Severinov et al., published June 1998, thus three months before the September 30, 1998, priority date accorded the instant application, disclose, see pages 16205-06 and

Figure 1, preparation of a labeled expressed protein using a pCYB2 plasmid having a multiple cloning site comprising a nucleic acid sequence that encoded a linker dipeptide between a carboxyl terminal amino acid of a desired polypeptide and the amino terminus of a modified *Sce* VMA intein, and further providing a nucleic acid sequence encoding a chitin binding protein fused to the cleavage-resistant carboxyl terminus of the modified *Sce* VMA intein, from which they obtained expressed proteins having a C-terminal thioester upon thiol reagent-induced cleavage of the intein, using a variety of the reagents recited in claim 14 herein, to which they ligated a flourescein-labeled peptide comprising a amino terminal cysteine, anticipating claims 12-14, 17-19, 25 and 26 herein. Severinov et al. also disclose, pages 16207-09 and Figure 2, preparation of an inactive expressed protein, the first 566 amino acids of the *E. coli* RNA polymerase σ^{70} subunit, using the pCYB2 plasmid having a multiple cloning site which they obtained expressed inactive proteins having a C-terminal thioester upon thiol reagent-induced cleavage of the modified *Sce* VMA intein to which they ligated a synthetic peptide having an amino-terminal cysteine and the next 34 amino acids of the polymerase σ^{70} subunit, restoring its activity, thus anticipating claims 12-14, 17-19 and 22 herein. The rejection of record is sustained.

Claims 12-14, 17, 18, 22, 25 and 26 are rejected under 35 U.S.C. §102(a) as being anticipated by Muir et al., 1988, of record.

Muir et al., published in June 1998, thus three months before the September 30, 1998, priority date accorded the instant application, disclose, pages 6706-09 and Figures 1-4, preparation of a labeled expressed protein using a pCYB2 plasmid having a multiple cloning site and further providing a nucleic acid sequence encoding a chitin binding protein fused to the cleavage-resistant carboxyl terminus of the modified *Sce* VMA intein, from which they obtained expressed proteins having a C-terminal thioester upon thiol reagent-induced cleavage of the intein to which they ligated a flourescein-labeled undecapeptide comprising a amino terminal cysteine, anticipating claims 12-14, 17-19, 25 and 26.

Muir et al. further disclose that the expressed protein, a C-terminal Src kinase, having a C-terminal thioester upon thiol reagent-induced cleavage of the modified *Sce* VMA was barely active with its native substrates but that ligation of the synthetic undecapeptide having an amino-terminal cysteine and a consensus sequence of conserved activating phosphorylation sites Src kinases greatly augmented its activity, thus anticipating claims 12-14, 17-19 and 22 herein. The rejection of record is sustained.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential §§35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 15, 17, 18, 23 and 24 are for reasons of record rejected under 35 U.S.C. §103(a) as obvious over Comb et al. as applied to claims 12-14, 16, 17 above, in view of Chong et al., 1997, discussed above with reference to claims 12-14, 17 and 18, and Severinov et al., discussed above with reference to claims 12-14, 17-19 and 22.

The disclosure of Comb et al. is taken as before and the further teaching of Comb et al., col. 77 at lines 52-54, that "[t]his method can be utilized to synthesize as functional proteins such as enzymes that are toxic to host cells" and this teaching is combined with those of Chong et al., 1997, of preparation of pCYB plasmids for recombinant expression of target proteins including several restriction endonucleases, see Table 1 at page 277 - which are enzymes inherently cytotoxic to any host cell in which they are expressed in the absence of expression of a corresponding, protective, methylase - fused to a modified *Sce* VMA intein which, in turn is fused via an uncleavable intein carboxyl terminus to the chitin

binding protein, permitting ready isolation of the purified restriction endonucleases. The further teaching of Chong et al., 1997, at page 279, left column of text, that "thiol esters that result from intein-mediated cleavage induced by thiol compounds can serve as intermediates in peptide ligation" is also emphasized. Also emphasized are the teachings of Severinov et al. of the division of the amino acid sequence of an enzyme subunit into a larger, inactive, portion for recombinant expression utilizing a pCYB plasmid and subsequent generation of a C-terminal thioester upon cleavage of the modified intein with a thiol reagent together with the solid-phase synthesis of a smaller, peptide portion comprising an amino-terminal cysteine for ligation to the larger, inactive, expressed portion to restore enzymatic activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to recombinantly express an inactive, truncated, restriction endonuclease by a method comprising preparing a plasmid according to claims 17 and 18 and obtaining the expressed inactive, truncated, restriction endonuclease with a C-terminal thioester upon cleavage of the *Sce* VNA modified intein with a thiol reagent according to claims 12-15 and to prepare a synthetic peptide comprising the remaining amino acid sequence of the restriction endonuclease with an amino terminal cysteine and to then ligate the synthetic peptide *in vitro* to the expressed inactive, truncated, restriction endonuclease with a C-terminal thioester to restore the activity of the restriction endonuclease. This is because Comb et al. teach that their method should be used to produce toxic proteins and Chong produced restriction endonuclease in low yields with a method similar to, and a plasmid similar to, that of Comb et al. due to the toxicity of these enzymes to the host cells where Chong et al. acknowledge that "thiol esters that result from intein-mediated cleavage induced by thiol compounds can serve as intermediates in peptide ligation" and because Severinov et al. show how to divide the amino acid sequence of an enzyme into a larger,

inactive, portion for recombinant expression utilizing a pCYB plasmid and subsequent generation of a C-terminal thioester upon cleavage of the modified intein with a thiol reagent together with the solid-phase synthesis of a smaller, peptide portion comprising an amino-terminal cysteine for ligation to the larger, inactive, expressed portion to restore enzymatic activity, demonstrating that this method is predictable and efficacious. The rejection of record is sustained.

Claims 12-14 and 17-19 are for reasons of record rejected under 35 U.S.C. §103(a) as being anticipated by Chong et al., 1997, as applied to claims 12-14 and 17-19 above, in view of Telenti et al., 1997, of record.

The teachings of Chong et al. are taken as before. Telenti et al. disclose a modified intein comprising a mutant *Mycobacterium xenopi GyrA* intein that is, see results depicted in Table 1 with the C114R mutant in the "MIEP" expression construct at page 6380, capable of thiol reagent-induced cleavage producing a thioester at the carboxyl-terminus of a polypeptide fused to the intein within a precursor protein which inherently may serve as target protein upon cleavage. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the modified *Mxe* GyrA intein of Telenti et al. for the modified Sce VMA intein of Chong et al. in practicing the methods of claims 12-14 and 17-19 as they had been practiced by Chong et al. because Telenti et al. demonstrate to such an artisan at that time that their modified *Mxe* GyrA intein is capable of producing a thioester at the C-terminus of a polypeptide fused to an intein within a precursor protein when contacted with a thiol reagent to cleave the intein, thus suitable in the methods of claims 12-14 and 17-19. The rejection of record is sustained.

Allowable Subject Matter

Claims 20 and 21 are objected to as being dependent upon a rejected base claim but remain free of the prior art of record herein and free of the non-statutory double-patenting rejections herein.

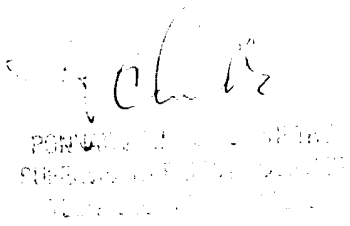
Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM-5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
May 17, 2003



Notice of References Cited	Application/Control No. 09/786,009	Applicant(s)/Patent Under Reexamination XU ET AL.	
	Examiner William W. Moore	Art Unit 1652	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Smith, D.R., et al., 1997, "Complete genome sequence of Methanobacterium thermoautotrophicum .delta.H: Functional analysis and comparative genomics", The Journal of Microbiology, Vol. 179, pages 7135-7155, see Fig. 8 at page 7152.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.